betes mellitus who has a history of many bacterial infections. The exposure of a chronic plantar ulcer to sand at a bathhouse infested with non-O1 *V cholerae* is the probable mechanism of entry that led to necrotizing fasciitis and septic shock. The history of pain out of proportion to physical findings suggested a deeper infection of the fascia that spread rapidly and resulted in septic shock. The inability to control necrotizing fasciitis despite surgical intervention often leads to amputation of extremities or death with involvement of abdominal or chest wall fascia. An aggressive medical-surgical team approach is necessary for the survival of the patient.

REFERENCES

1. Blake PA, Weaver RE, Hollis DG: Diseases of humans (other than cholera) caused by vibrios. Annu Rev Microbiol 1980; 34:341-367
2. Hennessy MJ, Ballon-Landa GR, Jones JW, Farrell T: *Aeromonas hydrophila* gas gangrene: A case report of management with surgery and hyperbaric oxygenation. Orthopedics 1988; 11:289-293
3. Blake PA, Allegra DT, Snyder JD, et al: Cholera—A possible endemic focus in the United States. N Engl J Med 1980; 302:305-309
4. Siegel MI, Rogers AI: Fatal non-O1 *Vibrio cholerae* septicemia in chronic lymphocytic leukemia. Gastroenterology 1982; 83:1130-1131
5. Wilson R, Lieb S, Roberts A, et al: Non group O1 *Vibrio cholerae* gastroenteritis associated with raw oysters. Am J Epidemiol 1983; 114:293-298
6. Morris JG Jr, Black RE: Cholera and other vibrioses in the United States. N Engl J Med 1985; 312:343-350
7. Hughes JM, Hollis DG, Gangarosa EJ, Weaver RE: Non-cholera vibrio infections in the United States—Clinical, epidemiologic, and laboratory features. Ann Intern Med 1978; 88:602-606
8. Smith HL Jr: Serotyping of non-cholera vibrios. J Clin Microbiol 1979; 10:85-90
9. Guard RW, Brigden M, Desmarchelier P: Fulminating systemic infection caused by *Vibrio cholerae* species which does not agglutinate with O-1 *V cholerae* antiserum. Med J Aust 1980; 1:659-661
10. Rabadan PM, Vilalta E: Non-O:1 *Vibrio cholerae* bacteremia (Letter). Rev Infect Dis 1989; 11:667
11. Platia E, Vosti KL: Noncholera vibrio septicemia. West J Med 1980; 132:354-357
12. Hansen W, Crokaert F, Yourassowsky E: Two strains of *Vibrio* species with unusual biochemical features isolated from ear tracts. J Clin Microbiol 1979; 9:152-153
13. Pitrak DL, Gindorf JD: Bacteremic cellulitis caused by non-serogroup O1 *Vibrio cholerae* acquired in a freshwater inland lake. J Clin Microbiol 1989; 27:2874-2876
14. Gelbart SM, Prabhudesai MM: *Vibrio cholerae* non-O1 cellulitis. Arch Pathol Lab Med 1986; 110:1182-1183
15. Peterson EM, Jemison-Smith P, de la Maza LM, Miller D: Cholecystitis: Its occurrence with cholelithiasis associated with a non-O1 *Vibrio cholerae*. Arch Pathol Lab Med 1982; 106:300-301
16. Fearrington EL, Rand CH, Mewborn A, Wilkerson J: Non-O1 vibrio septicemia and meningoencephalitis (Letter). Ann Intern Med 1974; 81:401
17. Robins-Browne RM, Still CS, Isaacson M, Koornhof HJ, Appelbaum PC, Scragg JN: Pathogenic mechanisms of anon-agglutinable *Vibrio cholerae* strain: Demonstration of invasive and enterotoxigenic properties. Infect Immun 1977; 18:542-545
18. McCardell BA, Madden JM, Shah DB: Isolation and characterization of a cytolysin produced by *Vibrio cholerae* serogroup non-O1. Can J Microbiol 1985; 31:711-720
19. Hase CC, Finkelstein RA: Comparison of the *Vibrio cholerae* hemagglutinin/protease and the *Pseudomonas aeruginosa* elastase. Infect Immun 1990; 58:4011-4015
20. Dhar R, Ghafoor MA, Nasralah AY: Unusual non-serogroup O1 *Vibrio cholerae* bacteremia associated with liver disease. J Clin Microbiol 1989; 27:2853-2855
21. Yang PM, Huang GT, Lin JT, et al: Ultrasonography in the diagnosis of benign diffuse parenchymal liver disease: A prospective study. Taiwan I Hsueh Hui Tsa Chih [J Formosa Med Assoc] 1988; 87:966-977
22. DeMeo AN, Andersen BR: Defective chemotaxis associated with a serum inhibitor in cirrhotic patients. N Engl J Med 1972; 286:735-740

Hyperammonemia With Severe Methanol Intoxication

WILLIAM A. FOSTER, MD
JOSEPH A. SCHOENHALS, MD
Salt Lake City, Utah

METHANOL POISONING leads to a well-described syndrome of metabolic acidosis with elevated anion gap and osmolar gap, vision impairment often leading to blindness, and in severe cases, progressive central nervous system dysfunction, renal and hepatic failure, and death.[1,2] The neurologic damage brought about by methanol poisoning, particularly that of the vision system, has been ascribed to the effects of formic acid, the principal toxic metabolite of methanol. Hyperammonemia, to our knowledge, has not been reported as a presenting feature of methanol toxicity. We report a case of severe methanol poisoning associated with hyperammonemia in the presence of near-normal liver function test results.

Report of a Case

The patient, a previously healthy 16-year-old boy, presented to the emergency department with symptoms of impaired vision and stupor. Two nights before admission, according to his family, the patient had been out drinking with friends. Subsequent investigation revealed that he had ingested methanol intended for use as a cleaning solvent but unaccountably stored in a vodka bottle. On the day before admission, the patient felt ill and vomited several times, but ascribed his symptoms to a hangover. On the day of admission, he was too ill to attend school and continued to have nausea and vomiting. While watching television that evening, he complained that he "couldn't see" and became progressively somnolent. On arrival at the emergency department, he was able to stand with assistance, but within moments of arrival became obtunded and had an apparent seizure. An endotracheal tube was inserted and supportive care begun.

The patient's initial vital signs included a blood pressure of 169/125 mm of mercury and a heart rate of 100 beats per minute. Arterial blood gas measurements with the patient receiving bag ventilation with 100% oxygen revealed a pH of 6.84, a P_{CO_2} of 19 mm of mercury, a P_{O_2} of 456 mm of mercury, and a calculated base excess of −31.3 mEq per liter. Diazepam and phenytoin were given to prevent further seizures. Administering

(Foster WA, Schoenhals JA: Hyperammonemia with severe methanol intoxication. West J Med 1995; 163:377-379)

From the Departments of Anesthesiology (Dr Foster) and Internal Medicine (Dr Schoenhals), Salt Lake Regional Medical Center, Salt Lake City, Utah.

Reprint requests to William A. Foster, MD, Salt Lake Regional Medical Center, 1050 E South Temple, Salt Lake City, UT 84102-9989.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
LDH = lactate dehydrogenase

intravenous naloxone hydrochloride and a solution of 50% dextrose in water produced no improvement in his mental state. The combination of severe metabolic acidosis, disturbed vision, and coma strongly suggested a diagnosis of methanol toxicity, and empiric therapy, including fluid resuscitation, ethanol infusion, and sodium bicarbonate infusion, was instituted. Pending the results of toxicology screens, the patient also received intravenous ceftriaxone sodium and acyclovir. Serum and urine toxicology screens were negative for ethanol, opiates, acetaminophen, salicylates, barbiturates, cocaine, and benzodiazepines.

The patient's serum methanol concentration on admission was 35 mmol per liter (113 mg per dl). A complete blood count was remarkable for a leukocyte count of 21.4 × 10^9 per liter (21,390 per mm^3), a hematocrit of 0.58 (58%), and a platelet count of 467 × 10^9 per liter (467,000 per mm^3). A blood chemistry profile gave the following values: sodium, 138, potassium, 4.7, and chloride, 97 mmol per liter; carbon dioxide, 4 mmol per liter; blood urea nitrogen, 6.8 mmol per liter (19 mg per dl); creatinine, 141 mmol per liter (1.6 mg per dl); and glucose, 14.3 mmol per liter (258 mg per dl). A serum lactate level was 11.2 mmol per liter. Liver function tests elicited the following values: aspartate aminotransferase (AST), 18 U per liter; alanine aminotransferase (ALT), 18 U per liter, γ-glutamyl transferase, 11 U per liter; lactate dehydrogenase (LDH), 181 U per liter; and alkaline phosphatase, 141 U per liter. Serum osmolality was 367 mOsm per kg (normal range, 278 to 305). Urinalysis revealed a specific gravity reported as "greater than 1.030" but was otherwise normal. A serum ammonia level, fortuitously measured on admission to rule out hepatic encephalopathy, was 347 μmol per liter (normal range, 7 to 27).

Hemodialysis was instituted on the night of admission. Despite aggressive supportive and specific therapy, the patient's hospital course was one of continued deterioration of multiple organ systems. The patient remained comatose; no further seizures were noted. Metabolic acidosis persisted despite dialysis and continued sodium bicarbonate infusion. The serum creatinine level rose to 230 mmol per liter (2.6 mg per dl) within 24 hours of admission and reached 504 mmol per liter (5.7 mg per dl) by the fourth hospital day. Profound hypokalemia developed, with serum potassium values remaining around 1.5 to 2.5 mmol per liter despite massive repletion. Coagulopathy developed, with prothrombin times increasing from 16.2 to 20.3 seconds and partial thromboplastin times from 39.9 to 56.1 seconds over the first 24 hours. Coagulopathy persisted despite replacement therapy. By the fourth day, the serum AST level had risen from 18 to 270 U per liter, the ALT level from 12 to 81 U per liter, and the LDH value from 181 to 1,418 U per liter.

When initially intubated, the patient demonstrated remarkable hyperventilation, with spontaneous minute ventilation often exceeding 40 liters per minute; yet, within six hours complete ventilatory support was necessary. Hemodynamic instability developed on the night of admission, with the patient becoming severely hypotensive (blood pressure, 60/30 mm of mercury) despite the administration of massive amounts of crystalloid and colloid solutions and the infusion of dopamine. A pulmonary artery catheter was placed, and the pulmonary capillary wedge pressure was maintained in the range of 10 to 16 mm of mercury. An echocardiogram revealed a small pericardial effusion and normal ventricular function. Additional infusions of phenylephrine hydrochloride, epinephrine, and norepinephrine bitartrate were required to maintain a systolic blood pressure of 80 to 90 mm of mercury. Serum ammonia levels were 55 and 63 mmol per liter on the second and third hospital days, respectively. By the fourth hospital day, the patient's condition had deteriorated to the point where meaningful recovery was deemed impossible. With the family's consent, life support was withdrawn, and the patient died.

Discussion

This unfortunate patient had a clinical course characteristic of severe methanol poisoning. An unusual feature of this case was a greatly elevated serum ammonia level on admission. Hyperammonemia persisted for at least two days despite hemodialysis, indicating an ongoing impairment of ammonia clearance. It is particularly interesting that the high initial ammonia level was found well before the development of catastrophic hepatic and renal failure.

Ammonia is a highly toxic by-product of amino acid catabolism and is normally cleared rapidly by its incorporation into urea.[3] Hyperammonemia results from either increased protein breakdown or impaired ureagenesis. In clinical practice, it is seen most often in patients with cirrhosis, especially in those with gastrointestinal bleeding. It is also a feature of Reye's syndrome. The diagnosis of Reye's syndrome was considered in this case, but was rejected on several grounds: there was no history of an antecedent viral illness; toxicology screens were negative for salicylates; there was no increase in serum aminotransferase levels until the third hospital day, as opposed to the early massive increase seen in Reye's syndrome; and the patient was hyperglycemic on admission, whereas normoglycemia or hypoglycemia is typical of Reye's syndrome.[4] Rhabdomyolysis, which has been reported as a complication of methanol poisoning (albeit without mention of hyperammonemia),[5] is a possible source of excess ammonia through the breakdown of muscle protein. Although specific evidence for rhabdomyolysis, such as serum creatine kinase measurement, was not sought, the absence of a positive hemoglobin test on the initial urinalysis makes substantial myoglobinuria unlikely.

Genetic defects involving enzymes of the urea cycle, such as ornithine transcarbamoylase or carbamoylphosphate synthetase, are possible causes of hyperammonemia.[3] These defects, however, present distinctive clinical syndromes in the neonatal period and are unlikely diagnoses in an otherwise healthy 16-year-old.

Interestingly, hyperammonemia with normal liver function is a frequent feature of several genetic syndromes involving errors of amino acid metabolism, grouped under the heading of "organic acidemias."[3,6,7] Examples include propionic, isovaleric, and methylmalonic acidemias. Hyperammonemia develops in these patients with organic acidemias even though all the enzymes of the urea cycle are present in normal amounts and function normally in vitro. There is experimental evidence that high levels of these organic acids,[8,9] or their coenzyme A esters,[10] can severely inhibit the conversion of ammonia into urea. Specifically, there is a decrease in the production of *N*-acetylglutamate, an allosteric activator of carbamoylphosphate synthetase. Carbamoylphosphate synthetase catalyzes the crucial reaction by which ammonia enters the urea cycle; a decrease in the amount of its activator (*N*-acetylglutamate) leads to a buildup of ammonia.

Because methanol toxicity can be regarded as an acquired organic acidemia (that is, formic acidemia), we speculate that formic acid may exert an indirect effect on ammonia clearance similar to that of the organic acids mentioned earlier. We further suggest that hyperammonemia may be an important and hitherto unappreciated contributor to the profound impairment of the central nervous system seen in patients with methanol poisoning. We encourage the early measurement of serum ammonia levels in suspected or confirmed cases of methanol toxicity, to help determine if this represents an isolated incident or a consistent feature of this disorder.

REFERENCES

1. Kruse JA: Methanol poisoning. Intensive Care Med 1992; 18:391-397

2. Agency for Toxic Substances and Disease Registry: Methanol toxicity. Am Fam Phys 1993; 47:163-171

3. Rezvani I, Auerbach VH: Urea cycle and hyperammonemia, *In* Behrman RE, Vaughan VC, Nelson WE (Eds): Nelson Textbook of Pediatrics, 13th edition. Philadelphia, Pa, WB Saunders, 1987, pp 297-301

4. Balistreri WF: Reye syndrome, *In* Behrman RE, Vaughan VC, Nelson WE (Eds): Nelson Textbook of Pediatrics, 13th edition. Philadelphia, Pa, WB Saunders, 1987, pp 840-842

5. Grufferman S, Morris D, Alvarez J: Methanol poisoning complicated by myoglobinuric renal failure. Am J Emerg Med 1985; 3:24-26

6. Rosenberg LE, Fenton WA: Disorders of propionate and methylmalonate metabolism, *In* Scriver CR, Beaudet AL, Sly WS, Valle D (Eds): The Metabolic Basis of Inherited Disease. New York, NY, Health Professions Division, McGraw-Hill, 1989, pp 821-845

7. Sweetman L: Branched chain organic acidurias, *In* Scriver CR, Beaudet AL, Sly WS, Valle D (Eds): The Metabolic Basis of Inherited Disease. New York, NY, Health Professions Division, McGraw-Hill, 1989, pp 791-821

8. Stewart PM, Walser M: Failure of the normal ureagenic response to amino acids in organic acid-loaded rats. J Clin Invest 1980; 66:484-492

9. Glasgow AM, Chase HP: Effect of propionic acid on fatty acid oxidation and ureagenesis. Pediatr Res 1976; 10:683-686

10. Coude FX, Sweetman L, Nyhan WL: Inhibition by propionyl-coenzyme A of *N*-acetylglutamate synthetase in rat liver mitochondria—A possible explanation for hyperammonemia in propionic and methylmalonic acidemia. J Clin Invest 1979; 64:1544-1551

MELAS Syndrome

STEVEN J. KOGA, MD
MARIAN HODGES, MD, MPH
CATHERINE MARKIN, MD
PAUL GORMAN, MD
Portland, Oregon

MELAS IS THE SYNDROME OF *m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes.[1] It is one of a number of mitochondrial syndromes that share the common characteristics of encephalopathy and myopathy. Other mitochondrial diseases include *m*yoclonus and *e*pilepsy with *r*agged *r*ed *f*ibers (MERRF),[2] Kearns-Sayre syndrome,[3,4] and progressive external ophthalmoplegia.[5] In recent years these syndromes have been shown to be associated with specific mutations of mitochondrial DNA (mtDNA).[6-10] At the same time, more common conditions such as cardiomyopathy, aminoglycoside-induced ototoxicity, and some forms of diabetes mellitus also have been shown to be associated with mitochondrial DNA mutations.[11-19] These associations, and the recognition of "incomplete" forms of the above encephalopathic and myopathic syndromes, indicate that mitochondrial dysfunction may be underrecognized in the pathogenesis of a number of diseases.

We report the case of a patient with the MELAS syndrome. We use the case as a basis for discussing the current clinical and molecular understanding of the syndrome and to explore the probable role of mitochondrial mutations in other diseases.

Report of a Case

A 43-year-old woman presented to the emergency department in respiratory arrest after five tonic-clonic seizures. She had had lethargy with nausea, vomiting, and diarrhea for a week and slurred speech for two days before admission. The patient's husband reported that she had been healthy with the exception of exercise intolerance and hearing loss since childhood. Her family history was relevant for at least ten maternally related family members with some combination of hearing loss, small stature, and adult-onset diabetes mellitus. On physical examination she appeared ill, was of slight build, and was being sustained by mechanical ventilation. Her blood pressure was 80/50 mm of mercury, her heart rate 100 beats per minute, respiratory rate 24 breaths per minute, and temperature 38.1°C (100.6°F). She was unresponsive even to deep pain, and her lungs had bibasilar crackles.

Laboratory evaluation showed an arterial pH of 7.20;

(Koga SJ, Hodges M, Markin C, Gorman P: MELAS syndrome. West J Med 1995; 163:379-381)

From the Department of Medical Education, Providence Medical Center (Drs Koga and Markin), and the Division of General Internal Medicine (Dr Hodges) and the Biomedical Information Communication Center (Dr Gorman), Oregon Health Sciences University, Portland.

Reprint requests to Steven J. Koga, MD, Caldwell Internal Medicine PA, 1818 S 10th St, Caldwell, ID 83605.